II. Claim Objections

The Office objects to claims 16-22, 25, and 26, as including non-elected subject matter. Office Action, page 3. The claims have been amended to remove the non-elected subject matter. Applicants respectfully request that the objection be withdrawn.

III. Indefiniteness Rejection

The Office rejects claim 19, under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Office Action, page 4. As noted by the Office, claim 19 is directed to recombinant viruses comprising two nucleic acids selected from among three groups of nucleic acids (designated groups (a), (b), and (c)). According to the Office, however, when the non-elected subject matter is removed from claim 16 (from which claim 19 depends), only group (a) remains in the claims. Thus, it is not clear to the Office what the second nucleic acid is in claim 19.

Applicants disagree. The viruses of claim 16 (from which claim 19 depends) comprise a nucleic acid selected from those "encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*," (*i.e.*, group (a)). According to MPEP 2111.03,

> The transitional term "comprising", . . . is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, *e.g.*, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *additional citations omitted*.

The open-ended "comprising" language of claim 16 does not preclude the inclusion of additional nucleic acids in the claimed viruses. Thus, it is permissible for Applicants to recite additional nucleic acids in the claims. To better clarify the claim, Applicants have

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amended claim 19 to recite viruses that "further comprise" a second nucleic acid encoding a mutated form of p53 (*i.e.*, group (a)). Thus, claim 16 is directed to a recombinant virus comprising two nucleic acids from group A. Groups (b) and (c) have been deleted from the claim, pending the outcome of Applicants petition to withdraw the restriction requirement. Applicants contend there is nothing indefinite about the inclusion of a second group (a) nucleic acid in the claimed recombinant viruses and respectfully request that the rejection be withdrawn.

IV. Obviousness Rejection

The Office rejects claims 16, 17, 19, 20-22, 25, and 26, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Michalovitz *et al.* (*Cell*, 62:671-690, 1991) in view of Moberg *et al.* (*J. Cell. Biochem.*, 49:208-215, 1992) and Le Gal La Salle *et al.* (*Science*, 259:988-990, 1993). Office Action, pages 4-6.

According to the Office, Michalovitz describes a temperature sensitive mutant of murine p53, and its transfection into rat embryo fibroblasts. Office Action, page 5. The Office notes that Michalovitz characterizes the p53val153 as suppressing transformation at 32.5ºC, but not at a higher temperature. *Id.* The Office admits that Michalovitz does not teach or suggest any virus containing mutant p53. *Id.* Applicants also note that Michalovitz does not teach or suggest the inhibition of neuronal cell degeneration.

The Office cites Moberg as teaching that mutant p53 does not suppress transcription from the c-myc promoter. Office Action, page 5. The Office also contends that this reference describes cotransfection of c-myc promoter with expression vectors expressing wild-type or mutant p53 protein. *Id.* Like Michalovitz, however, Applicants

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note that Moberg does not teach or suggest any virus containing mutant or wild-type p53, or the inhibition of neuronal cell degeneration.

To provide a teaching relating to adenoviral vectors, the Office cites Le Gal La Salle. Office Action, page 5. According to the Office, this reference describes a replication-deficient adenoviral vector for transferring genes to neurons and glial cells of the brain. *Id.* Applicants note that the reference only describes the transfer of a β-galactosidase gene using an adenoviral vector. Le Gal La Salle, pages 988-989. The Office points out several advantages of adenoviruses stated in Le Gal La Salle, including accommodation of larger inserts, larger host range, low human pathogenicity, and the ability to produce high titers. Office Action, page 5. Applicants contend that Le Gal La Salle does not teach or suggest any form of p53, however, or the inhibition of neuronal cell degeneration.

Based on the teachings of these three references, the Office concludes that it would be obvious to make an adenoviral vector described by Le Gal La Salle containing the mutant p53 described by Michalovitz, and express the vector in a glial or neuronal cell. *Office Action*, page 5.

To establish a *prima facie* case of obviousness, there must be some teaching, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to modify or combine the teachings of the references in the manner proposed by the Office. *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); M.P.E.P. § 2143. The suggestion or motivation must be found in the prior art, not in Applicant's disclosure. *Id.* And the suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed.

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Cir. 1999). While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Applicants respectfully traverse this rejection because the Office has not established a *prima facie* case of obviousness. In particular, the Office has failed to point to a clear and particular teaching that would motivate one of skill in the art to make the proposed combination of references to derive the presently claimed invention.

In an attempt to identify the requisite motivation to combine the cited references, the Office contends that Michalovitz and Moberg teach "different effects of mutant p53 and an artisan of skill would have been able to test the activity of the both wild type as well as mutant p53 using the same construct." *Office Action*, page 6. The Office seems to suggest that the skilled artisan would be motivated to test wild-type and mutant forms of p53 simply because they are known to have different biological activities. However, this statement does not provide any motivation to specifically provide mutant and wild-type p53 constructs in an adenoviral vector. Even if the motivation alleged by the Office did exist, which Applicants deny, one of skill in the art can readily test different forms of p53 without ever generating such a virus. In fact, both Michalovitz and Moberg prove this exact point, as they study and characterize p53 mutants without ever mentioning a viral vector.

At best, the Office's statement implies that it might be obvious to try such a combination, but that is not the standard for obviousness. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); M.P.E.P. § 2145(X)(B). A clear and particular teaching that

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provides a motivation to combine the specific teachings is required. Moreover, "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

With the benefit of hindsight, the Office also speculates that a mutant p53 construct could have been inserted into a viral vector because of some advantageous properties of adenoviruses mentioned by La Gal La Salle. Office Action, page 6. These advantageous properties, however, do not provide motivation to specifically select adenoviral vectors in the present case. La Gal La Salle listed the advantages of adenoviruses in a comparison with herpes simplex viruses, which are "limited by their poor efficiency of infection and their pathogenicity." La Gal La Salle, page 988. The reference does not teach or suggest that adenoviruses enjoy these same advantages over all other viral vectors.

Such a limited teaching does not justify the combination of references proposed by the Office. Recognizing that an adenovirus has a few advantages over a herpes virus does not motivate the skilled artisan to specifically select an adenoviral vector over all other vectors. The skilled artisan may consider numerous other (*i.e.*, non-adenoviral) viral vectors, as well as non-viral vectors, all of which possess various advantages and disadvantages in delivering and expressing a target gene. The cited art does nothing to motivate one of skill in the art to specifically select adenoviruses from all of these other possibilities. Thus, Applicants contend that there is no clear and specific motivation to make the combination of references proposed in this case. Consequently, the Office has failed to establish a *prima facie* case of obviousness.

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Claims 22, 25, and 26 are not *prima facie* obvious for another reason. Establishing a *prima facie* case of obviousness also requires that all the claim limitations be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); M.P.E.P. § 2143.03. With respect to the method claims claims 22, 25, and 26, Applicants contend that the combination of references proposed by the Examiner fails to teach or suggest all of the claim elements. As noted above, none of the references, alone or in combination, teach or suggest inhibition of neuronal cell death, as recited in the claims. Rather, the references implicate mutant p53 in cellular transformation and oncogenesis. Applicants contend that a method of inhibiting neuronal cell death is not taught or suggested by these teachings concerning transformation and oncogenesis. Thus, once again, the Office has not met a threshold requirement for establishing a *prima facie* case of obviousness.

In summary, the Office has failed to identify any teaching that would motivate one of skill in the art to combine the cited references in the proposed manner. Lacking a clear and particular teaching that establishes the requisite motivation, Applicants contend that the Office has failed to establish a *prima facie* case of obviousness. In addition, the proposed combination of references fails to teach or suggest all of the limitations of the claimed method (claims 22, 25, and 26). Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly

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solicited. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 9, 2002

By: _____

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APPENDIX

16. (Amended) A recombinant virus selected from the group consisting of adenovirus, adeno-associated virus and herpes virus, said recombinant virus comprising a nucleic acid [selected from the group consisting of:]

[(a) nucleic acids] encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*[;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53].

19. (Amended) A recombinant virus according to claim 16, wherein said virus <u>further</u> comprises [two] <u>a second</u> nucleic <u>acid</u> [acids selected from the group consisting of:

(a) nucleic acids] encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration[;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53].

22. (Amended) A method of inhibiting toxicity in cultured neuronal cells comprising administering to said cells a nucleic acid [selected from the group consisting of:]

[(a) nucleic acids] encoding a mutated form of p53 which antagonizes wild-type p53-mediated neuronal cell degeneration *in vitro*[;

(b) the site for binding of p53 to DNA; and

(c) nucleic acids encoding an antisense RNA which inhibits expression of p53].

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